

Remarks

As noted above, Applicant would like to point out that a Preliminary Amendment was filed on May 22, 2003, together with the Response to Restriction Requirement filed on the same date. However, it appears that the Preliminary Amendment was not entered, since the rejections in the Office Action mailed August 22, 2003, refer to the claims as they appeared prior to the Preliminary Amendment. Applicant respectfully requests entry of the Preliminary Amendment dated May 22, 2003, a copy of which is enclosed herein. A copy of the Transmittal Letter that was submitted with the Preliminary Amendment and Response to Restriction Requirement on May 22, 2003, is also enclosed. The present Amendments and Remarks are directed to the claims as they will appear after entry of the Preliminary Amendment.

The claimed invention

The present claims are drawn in part to compositions comprising inhibitors of fatty acid synthesis in an amount effective for the treatment of malaria. The claims are based on Applicant's discovery and characterization of a pathway for *de novo* synthesis of fatty acids in the malaria parasite and the subsequent discovery that compounds that inhibit this pathway are useful in the treatment and prevention of malaria. Certain claims are drawn to targets for treatment of malaria comprising components of a fatty acid synthesis pathway in a malarial parasite. Additional claims are drawn to novel compounds and compound combinations.

Amendments to the claims

Claim 7 has been amended to recite that the claimed antimalarial composition is in an amount effective for the treatment of malaria. As discussed further below in the remarks directed to the rejections under 35 U.S.C. § 102, Applicant showed that compositions comprising inhibitors of fatty acid synthesis, e.g., hydroxy substituted diphenyl ethers such as triclosan and the structurally unrelated compound cerulenin in certain amounts effectively inhibit growth of malaria parasites *in vitro* within human red blood cells (see, e.g., Examples 2, 3, and 4 at pp. 19-21 and Tables 1 and 2 at pp. 27 and 28). In addition, Applicant showed that compositions comprising the fatty acid inhibitor triclosan in certain amounts reduce parasitemia and prolong survival in mice infected with malaria parasites, using an accepted model for malaria infection (see, e.g., Example 5 at p. 22 and Table 3 at p. 28). These data provide support for the

amendment to claim 7 in that they disclose the existence of compositions comprising inhibitors of fatty acid synthesis in amounts effective for treatment of malaria and provide guidance as to appropriate dose ranges for use in human or animal subjects. Additional support is found throughout the specification (see, e.g., p. 7, "Summary of the Invention").

Claim 8 has been amended to improve clarity since useful pharmaceutically acceptable derivatives of inhibitors of fatty acid synthesis will themselves be inhibitors of fatty acid synthesis.

Claims 9 – 13 and 15 have been amended to enhance clarity and conform with United States claim drafting practice.

Applicant notes that claims 19 and 20 were included in Group I (the group presently under examination) and that the present Office Action contains no specific rejection of those claims. However, claim 17, on which claims 19 and 20 depend, was included in Group III. Applicant has accordingly amended claims 19 and 20 to incorporate the limitations of claim 17 and submits that these claims are presently in condition for allowance.

New claims 36 – 40 are drawn to particular compounds that fall within Formula 2 given in original claim 3 (claim 9 after entrance of the Preliminary Amendment). Original claim 3 specifically recites the limitations that "either R₁ or R₂ represent a hydroxy (OH) group and the other being a hydrogen atom, respectively, or both being hydroxyl groups" and "other positions (R₃ to R₁₀) of the phenyl rings I and II being substituted in various permutations and combinations by chlorine...or aldehyde or keto groups...". Support for the new claims is accordingly found therein. Neither Gump nor Model discloses such compounds.

New claim 41 is drawn to a subset of compounds disclosed in original claim 3 (claim 9 after entrance of the Preliminary Amendment), namely compounds (thioesters) in which the two phenyl rings are joined by an S atom. Original claim 3 specifically claims compounds of Formula 2 in which "optionally the two phenyl rings being joined by a sulfur atom (X=S)". New claim 41 is drawn to such compounds, which are not disclosed by either Gump or Model.

New claim 42 is drawn to a subset of compounds disclosed in original claim 3 (claim 9 after entrance of the Preliminary Amendment), namely compounds (thioesters) in which the two phenyl rings are joined by a CH₂ group. Original claim 3 specifically claims compounds of Formula 2 in which "optionally the two phenyl rings being joined by a sulfur atom (X=S) or by a

methylene (X = CH₂) group”. New claim 42 is drawn to such compounds, which are not disclosed by either Gump or Model.

New claim 43 replaces claim 14, and support for the new claim is found in previously presented claim 14.

New claims 44 - 49 recite combinations of compounds. Support for these claims is found in claim 8 and in teachings throughout the specification that hydroxydipheyl ethers, including triclosan, are inhibitors of fatty acid synthesis. Additional support is found at p. 3, lines 17-18 and at p. 4, line 4 (for known antimalarials) and at p.17, lines 3-7 (for cerulenin).

New claim 50 recites a combination of triclosan and cerulenin. Support for this claim is found at p. 17, lines 15-16, and on p. 28.

Rejections under 35 U.S.C. § 112

Claims 9-13, 15, 16, 19 and 20 stand rejected under 35 U.S.C. § 112 as being indefinite on the ground that the claims depend on cancelled claim 1. As discussed in the Remarks, in a Preliminary Amendment filed May 22, 2003, these claims were amended to remove the dependencies on cancelled claims. Applicant has herein requested entry of the Preliminary Amendment and submits that the claims as amended therein are no longer dependent on a cancelled claim. Applicant respectfully requests withdrawal of the rejection.

Claim 14 stands rejected under 35 U.S.C. § 112 on the ground that the phrase “including” renders the claim indefinite. Claim 14 has been canceled and replaced by new claim 42, which is similar to claim 14 but does not contain the word “including”. Applicant respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. § 102

Claims 7-14 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,428,951, to 2,250,480, to Gump, hereinafter “Gump” and U.S. Patent No. 3,506,720, to Model *et al.*, hereinafter “Model”. Applicants respectfully traverse this rejection.

Claim 7 has been amended to recite that the claimed composition is in an amount effective for the treatment of malaria. As described on pp. 9 and 16 in the instant application and elsewhere throughout the document Applicant made the ground-breaking discovery of the existence of a *de novo* fatty acid synthesis pathway in malaria parasites (e.g., *P. falciparum*). Prior to Applicant’s discovery it was assumed that the malaria parasite utilized fatty acids

produced by the host. Furthermore, Applicant discovered the unexpected fact that the fatty acid synthesis pathway in malaria parasites employs the dissociated fatty acid synthases, i.e., type II fatty acid synthase, unlike the type I fatty acid synthases utilized by mammalian cells in which a multiprotein complex is employed. Certain of Applicant's discoveries are also described in a scientific article published in *Nature Medicine* by Applicant (included herein as Exhibit A), further attesting to the significance of Applicant's work.

Applicant further discovered that inhibitors of fatty acid synthesis, e.g., compounds that inhibit enzymes in the fatty acid synthesis pathway, are effective against malaria parasites. Applicant tested such compounds both *in vitro* and *in vivo* and identified concentration ranges that are effective in inhibiting growth of the malaria parasite *in vitro* and in prolonging the survival of mice infected with malaria. For example, as described in Examples 2, 3, and 4, at pp. 19-22 of the application, Applicant showed in an *in vitro* system in which red blood cells were infected with malaria parasites, that the IC₅₀ (concentration needed to inhibit growth of the parasite by 50%), of an exemplary fatty acid synthesis inhibitor, triclosan, is between approximately 0.7 μ m and 0.8 μ m. These numbers were determined by microscopic examination, by measuring protein synthesis as evidenced by incorporation of ³⁵S methionine into protein (see Figure 1 and Table 1, p. 27), and by measuring nucleic acid synthesis as evidenced by ³H hypoxanthine incorporation into nucleic acids (see Table 2, pl 28). Furthermore, as indicated in Exhibit A (see Figure 1a, on p. 168), a lower concentration of approximately 0.3 μ m was effective in inhibiting protein synthesis by approximately 15 – 20%, while higher concentrations such as 1.2 μ m almost completely eliminated parasite growth. These *in vitro* assays are of particular significance since they were performed in a system in which the parasites are present within human red blood cells in a liquid medium rather than merely cultured in an isolated state. In addition, as described in Example 4, Applicant has shown that a second inhibitor of fatty acid synthesis, cerulenin, has an IC₅₀ of 20 μ m when applied to malaria parasites.

Applicant has further shown that the fatty acid synthesis inhibitor triclosan possesses antimalarial activity *in vivo*. As described in Example 5, p. 22, Applicant administered various doses of triclosan to mice that had been previously infected with malaria parasites. As shown in Table 3, 4 daily injections at a dose of 3.0 mg/kg reduced parasitemia to approximately 20%, as compared with almost 70% in untreated animals. Furthermore, mice treated with 38 – 40 mg/kg

triclosan survived for prolonged periods (e.g., greater than 6 weeks, which represented the total follow-up time), whereas untreated counterparts died within 8 days of infection (p. 22, lines 8-12). The animal model for malaria infection used by Applicant has been widely used in the identification and study of accepted antimalarial agents for many years. (See, e.g., Peters, W., "Chemotherapy of Malaria", Kreir, J.P. (ed.), *Malaria*, Vol I., London: Academic Press, pp. 145-283, 1980; Warhurst, D.C. and Folwell, R.O., "Measurement of the growth rate of the erythrocytic stages of *Plasmodium berghei* and comparisons of the potency of inocula after various treatments. *Ann. Trop. Med. Parasitol.* 62, pp., 349-360, 1968; Owais, M., *et al.*, "Chloroquine encapsulated in malaria-infected erythrocyte-specific antibody-bearing liposomes effectively controls chloroquine-resistant *Plasmodium berghei* infections in mice", *Antimicrobial Agents and Chemotherapy*, 39, pp. 180-184, 1995. A copy of the latter is enclosed herein as Exhibit B.)

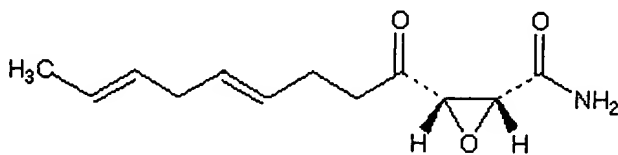
Applicant has thus provided extensive evidence for the existence of compositions comprising an inhibitor of fatty acid synthesis in an amount effective for the treatment or prevention of malaria. Such compositions are not disclosed or suggested by the prior art, which failed to recognize the efficacy of inhibitors of fatty acid synthesis for treatment or prevention of malaria. Applicant has provided explicit guidance as to the effective amounts and has provided explicit dose ranges based on studies in a mouse model for malaria infection. Neither Gump nor Model discloses or suggests such antimalarial compositions.

Furthermore, hydroxydiphenyl ether compounds such as triclosan have heretofore been used externally, e.g., as components in acne creams, toothpastes, soaps, and mouthwashes, or as disinfectants for household goods and other products, rather than internally as in the treatment or prevention of malaria (see Exhibit A, p. 170 (right column), mentioning use of triclosan "in the consumer industry ranging from children's toys to toothpastes, detergents, and soaps". The Examiner has not identified any prior art that teaches or suggests the use of such compounds for purposes of treating or preventing a systemic infection and certainly nothing that teaches or suggests the use of such compounds for malaria. Gump, for example, extensively discusses the use of his compounds for purposes such as "disinfection of personal and household linen...and...in bactericidal compositions, for instance, washing agents and liquors" (col. 1, lines 32-36). Model discusses use of his compounds as "non-irritant skin disinfectants and as fungicidal agents in the treatment of fungal dermatoses" (col. 2, lines 50-53). Neither of these

patents remotely suggests that the compounds disclosed therein would be effective against malaria parasites. Applicant, on the other hand, has provided both the motivation to employ this class of compounds for treatment and prevention of malaria and has provided evidence of efficacy, confirming the existence effective compounds and providing guidance as to dosage ranges. Applicant therefore respectfully requests withdrawal of the rejection.

Claim 8, as amended, is drawn to an antimalarial composition comprising an inhibitor of fatty acid synthesis in combination with one or more known antimalarials and a pharmaceutically acceptable adjuvant, diluent, or carrier. Applicant submits that neither Gump nor Model discloses or suggests the combination of an inhibitor of fatty acid synthesis together with a second compound effective for the treatment or prevention of malaria. The idea of combining an inhibitor of fatty acid synthesis with a second antimalarial agent arose directly from Applicant's discovery that inhibitors of fatty acid synthesis are effective against the malaria parasite. Prior to this discovery there would have been no motivation to combine an inhibitor of fatty acid synthesis with an antimalarial compound. Applicant recognized that such combinations may provide, for example, enhanced efficacy, synergistic effects, and/or increased likelihood of activity against drug-resistant malarial strains.

Claim 16 is dependent on claim 7. After entrance of the present Amendment, claim 16 will therefore be drawn to an antimalarial composition comprising cerulenin in an amount effective for treatment or prevention of malaria. The structure of cerulenin is presented below:



Applicant submits that this structure is distinct from those disclosed by Model and Gump and therefore respectfully requests withdrawal of the rejection of claim 16.

Applicant further points out that cerulenin is a fungal product that is a known inhibitor of fatty acid synthesis (see Exhibit C). Applicant's claim to an antimalarial composition comprising cerulenin in an amount effective to treat or prevent malaria is directly based on Applicant's discovery that inhibitors of fatty acid synthesis are effective for the treatment and prevention of malaria. While cerulenin itself is known in the art, prior to Applicant's

discoveries, one skilled in the art would have had no reason to believe that cerulenin would be effective for treatment or prevention of malaria and would have had no motivation to develop a composition comprising cerulenin in an amount effective to do so.

New claims 36-42 are drawn to novel compounds that are not anticipated by Gump or Model.

In light of the amendments presented herein, Applicant respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. § 103

Claim 15 stands rejected under 35 U.S.C. § 103 as being unpatentable over Gump and Model on the ground that determination of a dosage range having optimum therapeutic index is well within the level of one having ordinary skill in the art. The Examiner asserts that the skilled artisan would have been motivated to determine optimum dosage amounts to get the maximum effect of the composition. Applicant respectfully traverses this rejection.

Firstly, the Examiner has not provided any objective evidence to support the generalized and conclusory assertion that determination of a dosage range having optimum therapeutic index is well within the level of one having ordinary skill in the art. While the Examiner's contention that the claimed invention is obvious does not rely on a combination of references but instead relies solely on the alleged skill and motivation of one of ordinary skill in the art, the requirements to establish a *prima facie* case of obviousness based on prior art references are nonetheless relevant. According to MPEP §706.02(j), Contents of a 35 U.S.C. §103 Rejection, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

Applicant submits that neither Gump nor Model recognized that the compounds described in their patents might be useful for the treatment and/or prevention of malaria. Neither

patent remotely suggests such a use. The Examiner has not identified a single piece of prior art that suggests that the composition of claim 15, or any of the compounds recited in the instant claims, would be useful for the treatment or prevention of malaria. This teaching is to be found solely in the instant application itself and in Applicant's other work.

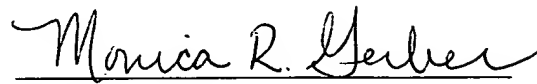
In order to determine the claimed dosage range Applicant conducted *in vitro* tests and then performed extensive experiments in animals using an accepted mouse model for assessing the efficacy of anti-malarial drugs. Applicant submits that one of ordinary skill in the art would have found no motivation in either Gump or Model to test the compounds either *in vitro* or in an animal model for malaria in order to determine an appropriate dosage range for this condition. The Examiner has thus made impermissible use of hindsight in maintaining that claim 15 is obvious. As the Court of Appeals for the Federal Circuit has stated, "Obviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor." *Para Ordnance Manufacturing, Inc.*, 73 F.3d 1085, 37 USPQ2d 1237 (Fed. Cir. 1995). Prior to Applicant's invention one of ordinary skill in the art would not even have recognized the existence of a pathway for the synthesis of fatty acids in malaria parasites and would therefore have had no motivation to even attempt to identify an optimum therapeutic index for compounds that inhibit synthesis of fatty acids in the treatment or prevention of malaria. It would not have been obvious even to try to inhibit this pathway in the complete absence of its existence, and there would have been no reasonable expectation of success in treating or preventing malaria by administering compounds that inhibit a pathway not even known to exist in malaria. Withdrawal of the rejection is respectfully requested.

In conclusion, in view of the amendments and remarks presented herein, none of the cited art anticipates any of the claims pending in the instant application nor renders them obvious, and the application complies with the requirements of 35 U.S.C. §112. Applicants therefore respectfully submit that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5000 or (617) 248-5071 (direct dial).

Please charge any fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,

A handwritten signature in cursive script, reading "Monica R. Gerber". The signature is written in dark ink and is positioned above a horizontal line.

Monica R. Gerber
Registration Number 46,724

Date: February 23, 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Surolia, N. <i>et al.</i>	Examiner: K. Weddington
Serial No.:	09/763,499	Art Unit: 1614
Filed:	February 23, 2001	
For:	USE OF HYDROXYDIPHENYL ETHER CLASS OF CHEMICALS, AS EXEMPLIFIED BY TRICLOSAN, AS AN ANTIMARIAL AND IDENTIFICATION OF FATTY ACID SYNTHESIS AS ITS TARGET	

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:


**TRANSMITTAL OF PRELIMINARY AMENDMENT AND RESPONSE TO
RESTRICTION REQUIREMENT**

In response to the Restriction Requirement mailed by the U.S. Patent and Trademark on March 5, 2003, enclosed herewith please find the following:

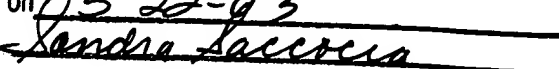
1. Response to Restriction Requirement (3 pp.)
2. Preliminary Amendment (14 pp.)
3. Petition for Extension of Time (1 p.)
4. Copy of Transmittal Letter for Filing of Patent Application under 35 U.S.C. 371 (2 pp.)
5. Check in the amount of \$205
6. Return Postcard

Additionally, please charge any further fees associated with this filing or apply any credits to our Deposit Account No. 03-1721.

Respectfully submitted,


Monica R. Gerber, M.D., Ph.D.
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Dated: May 22, 2003
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I hereby certify that this correspondence is being deposited
with the United States Postal Service as first class mail in
an envelope addressed to: Commissioner For Patents,
P.O. Box 1450, Alexandria, VA 22313
on 05-22-03


IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Surolia, N.

Examiner: Weddington, K.

Serial Number: 09/763,499

Art Unit: 1614

Filing Date: February 23, 2001

Attorney Docket: 2003710-0001
(IN99/00026)

Title: USE OF HYDROXYDIPHENYL ETHER CLASS OF CHEMICALS,
AS EXEMPLIFIED BY TRICLOSAN, AS AN ANTIMALARIAL
AND IDENTIFICATION OF FATTY ACID SYNTHESIS AS ITS
TARGET

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

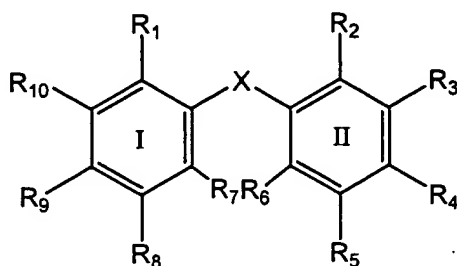
PRELIMINARY AMENDMENT

In the preliminary amendment filed February 23, 2001, Applicant cancelled claims 1-6 and filed claims 7-35. However, Applicant has become aware that some of the claims as presented in the Preliminary Amendment contained a typographical error resulting from the fact that claims 7-35 were originally drafted as claims 1-29. However, when the claims were renumbered as claims 7-35, certain dependencies were not renumbered to correspond with the new claim numbers. Thus certain of claims 7-35 that should be dependent on claim 7 are currently dependent on cancelled claim 1, while other claims that should be dependent on claim 17 are dependent on claim 10. An examination of the claim structure will make it clear that these are typographical errors and that their correction does not constitute the addition of new matter. Please amend the claims as follows to correct these errors.

A marked up version of the amended claims, showing changes made, is enclosed herein. For the Examiner's convenience, a copy of the complete set of claims as they will appear following entry of this Amendment is also enclosed as Appendix A.

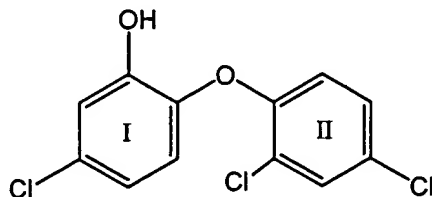
In the claims (Clean version)

9. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl ether of general formula 2 given below wherein the two phenyl rings (I & II) are joined by an oxygen ($X=O$) atom and either R_1 or R_2 represent a hydroxy (OH) group and the other being a hydrogen atom, respectively, or both being hydroxy groups and other positions (R_3 to R_{10}) of the phenyl rings I and II being substituted in various permutations and combinations by chlorine, bromine or iodine atoms or hydroxy, aldehyde or keto groups or hydrogen atoms or ester group and optionally the two phenyl rings being joined by a sulfur atom ($X=S$) or by a methylene ($X=CH_2$) group.



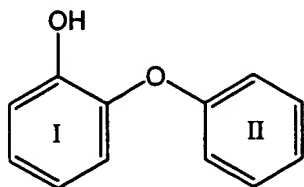
Formula 2

10. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl ether of general formula 2 represented by triclosan [2',4,4'-trichloro-2-hydroxydiphenyl ether which can also be written as 2,4,4''-trichloro-2'-hydroxydiphenyl ether. This is also named as 5-chloro-2-(2,4-dichlorophenoxy)phenol] of formula 1 given below:

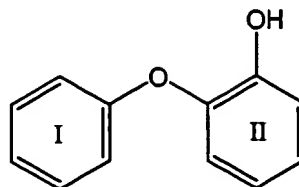


Formula 1

11. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl ether of general formula 2 represented by the compounds of formula 3 and 4 given below:

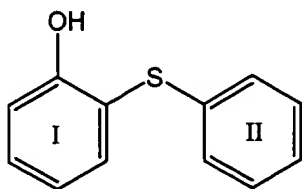


Formula 3

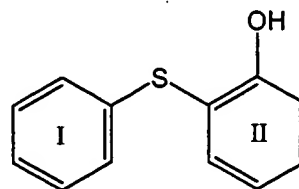


Formula 4

12. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl thioether analogs of general formula 2 represented by the compounds of formulas 5 and 6 given below:

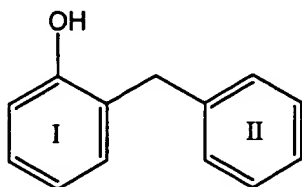


Formula 5

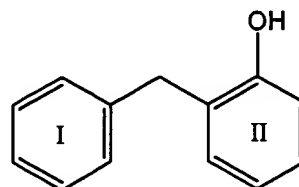


Formula 6

13. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl methane analogs (e.g. Chlorophenes) of general formula 2 represented by the compounds of formulas 7 and 8 given below:



Formulas 7



Formula 8

15. (Once amended) An antimalarial composition as claimed in claim 7 for treating a malarial condition wherein the amount of the fatty acid synthesis inhibitor used is in the dosage range of 0.03 mg/kg to 100 mg/kg of a human or an animal subject for treating a malarial condition.

16. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is cerulenin.

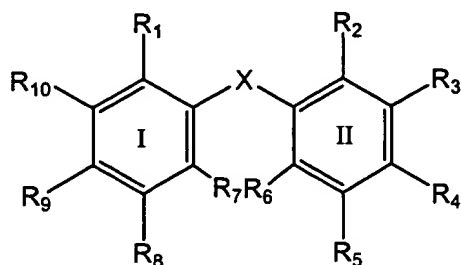
19. (Once amended) An antimalarial drug target as claimed in claim 17 wherein the malarial parasite used is *P. falciparum*.

20. (Once amended) An antimalarial drug target as claimed in claim 17 wherein the malarial parasite used is of human or animal origin.

25. (Once amended) A method of treatment of malaria in a subject, wherein the said method comprising the administration of the composition as claimed in claim 7 to the said subject through a route selected from the group consisting of oral, intramuscular, intradermal, intraperitoneal, intravenous, intra-arterial and subcutaneous.

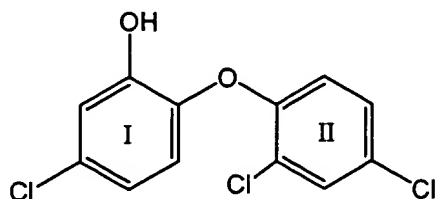
In the claims (Version with markings to show changes made)

9. (Once amended) An antimalarial composition as claimed in claim 7 [1] wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl ether of general formula 2 given below wherein the two phenyl rings (I & II) are joined by an oxygen (X=O) atom and either R₁ or R₂ represent a hydroxy (OH) group and the other being a hydrogen atom, respectively, or both being hydroxy groups and other positions (R₃ to R₁₀) of the phenyl rings I and II being substituted in various permutations and combinations by chlorine, bromine or iodine atoms or hydroxy, aldehyde or keto groups or hydrogen atoms or ester group and optionally the two phenyl rings being joined by a sulfur atom (X=S) or by a methylene (X=CH₂) group.



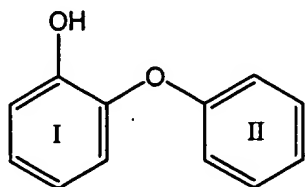
Formula 2

10. (Once amended) An antimalarial composition as claimed in claim 7 [1] wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl ether of general formula 2 represented by triclosan [2',4,4'-trichloro-2-hydroxydiphenyl ether which can also be written as 2,4,4''-trichloro-2'-hydroxydiphenyl ether. This is also named as 5-chloro-2-(2,4-dichlorophenoxy)phenol] of formula 1 given below:

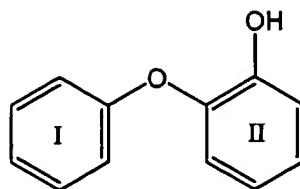


Formula 1

11. (Once amended) An antimalarial composition as claimed in claim 7 [1] wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl ether of general formula 2 represented by the compounds of formula 3 and 4 given below:

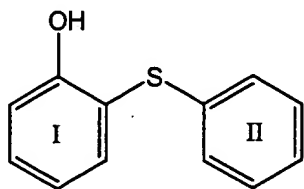


Formula 3

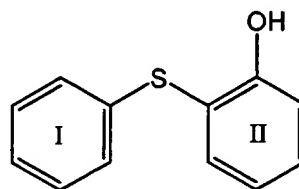


Formula 4

12. (Once amended) An antimalarial composition as claimed in claim 7 [1] wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl thioether analogs of general formula 2 represented by the compounds of formulas 5 and 6 given below:

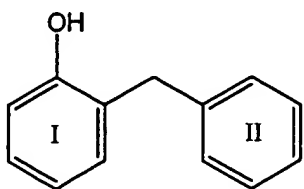


Formula 5

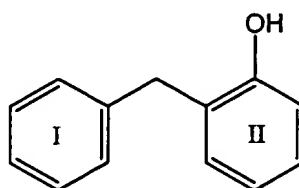


Formula 6

13. (Once amended) An antimalarial composition as claimed in claim 7 [1] wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl methane analogs (e.g. Chlorophenes) of general formula 2 represented by the compounds of formulas 7 and 8 given below:



Formulas 7



Formula 8

15. (Once amended) An antimalarial composition as claimed in claim 7 [1] for treating a malarial condition wherein the amount of the fatty acid synthesis inhibitor used is in the dosage range of 0.03 mg/kg to 100 mg/kg of a human or an animal subject for treating a malarial condition.

16. (Once amended) An antimalarial composition as claimed in claim 7 [1] wherein the inhibitor of fatty acid synthesis used is cerulenin.

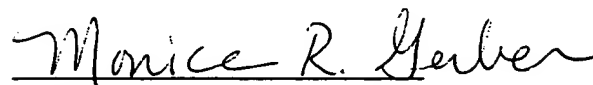
19. (Once amended) An antimalarial drug target as claimed in claim 17 [10] wherein the malarial parasite used is *P. falciparum*.

20. (Once amended) An antimalarial drug target as claimed in claim 17 [10] wherein the malarial parasite used is of human or animal origin.

25. (Once amended) A method of treatment of malaria in a subject, wherein the said method comprising the administration of the composition as claimed in claim 7 [1] to the said subject through a route selected from the group consisting of oral, intramuscular, intradermal, intraperitoneal, intravenous, intra-arterial and subcutaneous.

Please charge any additional fees that may be associated with this matter to our Deposit Account No. 03-1721.

Respectfully submitted,



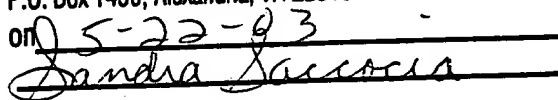
Monica R. Gerber, M.D., Ph.D.

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Dated: May 22, 2003

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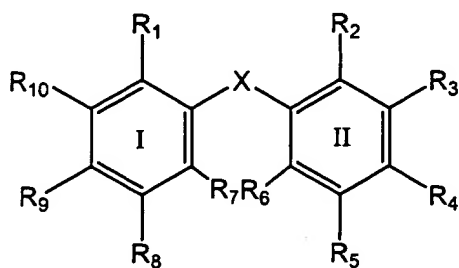
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Appendix A: Clean copy of all claims following entry of this Amendment.

In the claims

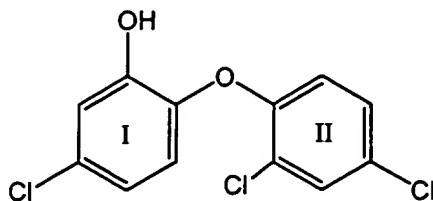
7. An antimalarial composition comprising an inhibitor of fatty acid synthesis of the malarial parasite for treating malaria.
8. An antimalarial composition comprising an inhibitor of fatty acid synthesis or its pharmaceutically acceptable derivatives either alone or in combination with one or more known antimalarials along with a pharmaceutically acceptable adjuvant or a diluent or a carrier.
9. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl ether of general formula 2 given below wherein the two phenyl rings (I & II) are joined by an oxygen (X=O) atom and either R₁ or R₂ represent a hydroxy (OH) group and the other being a hydrogen atom, respectively, or both being hydroxy groups and other positions (R₃ to R₁₀) of the phenyl rings I and II being substituted in various permutations and combinations by chlorine, bromine or iodine atoms or hydroxy, aldehyde or keto groups or hydrogen atoms or ester group and optionally the two phenyl rings being joined by a sulfur atom (X=S) or by a methylene (X=CH₂) group.



Formula 2

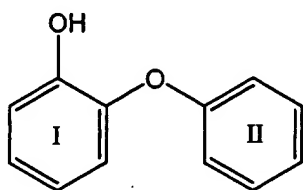
10. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl ether of general formula 2 represented by triclosan [2',4,4'-trichloro-2-hydroxydiphenyl ether which can also be written as 2,4,4''-trichloro-2'-

hydroxydiphenyl ether. This is also named as 5-chloro-2-(2,4-dichlorophenoxy)phenol] of formula 1 given below:

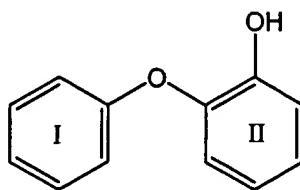


Formula 1

11. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl ether of general formula 2 represented by the compounds of formula 3 and 4 given below:

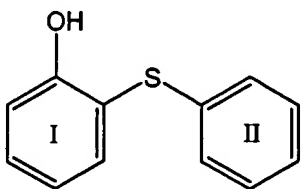


Formula 3

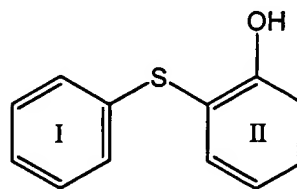


Formula 4

12. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl thioether analogs of general formula 2 represented by the compounds of formulas 5 and 6 given below:

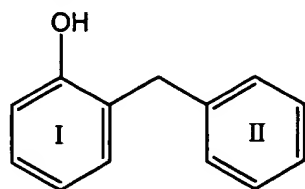


Formula 5

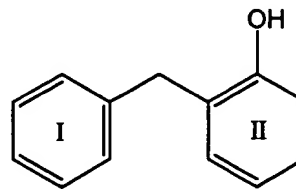


Formula 6

13. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is a hydroxydiphenyl methane analogs (e.g. Chlorophenes) of general formula 2 represented by the compounds of formulas 7 and 8 given below:



Formulas 7



Formula 8

14. An antimalarial composition consisting of a hydroxydiphenyl ether including triclosan for treating a malarial condition caused by a drugs resistant malarial parasite.

15. (Once amended) An antimalarial composition as claimed in claim 7 for treating a malarial condition wherein the amount of the fatty acid synthesis inhibitor used is in the dosage range of 0.03 mg/kg to 100 mg/kg of a human or an animal subject for treating a malarial condition.

16. (Once amended) An antimalarial composition as claimed in claim 7 wherein the inhibitor of fatty acid synthesis used is cerulenin.

17. An antimalarial drug target comprising a component of fatty acid synthesis pathway in a malarial parasite. The components comprise of (β -hydroxydecanoyl-ACP dehydrase or β -ketoacyl-ACP synthase I or malonyl-CoA: ACP transacylase or β -ketoacyl-ACP synthase II or β -ketoacyl-ACP reductase or β -ketoacyl-ACP-synthase III or enoyl-ACP reductase or β -hydroxyacyl-ACP dehydrase.

18. An antimalarial drug target comprising a component of fatty acid synthesis pathway where the component is enoyl-ACP reductase activity in a malarial parasite.

19. (Once amended) An antimalarial drug target as claimed in claim 17 wherein the malarial parasite used is *P. falciparum*.

20. (Once amended) An antimalarial drug target as claimed in claim 17 wherein the malarial parasite used is of human or animal origin.

21. A method of inhibiting the growth of human malaria parasite by the use of hydroxydiphenyl ether class of chemicals wherein the said method comprises the steps of:

- a. Examining smears of *in vitro* treated cultures for morphological features of the parasite as an indicator of growth; or
- b. Monitoring the incorporation of [³⁵S] methionine in proteins or [³H]hypoxanthine in nucleic acid as a quantitative indicator of the inhibition of the parasite growth.

22. A method of inhibiting the growth of malaria parasite in an animal, the said method comprising:

- a. Monitoring the extent of inhibition of parasitemia by examining the smears of a blood sample taken from an animal; or
- b. by determining the reduction in the mortality rate of the treated animal vs. untreated animal.

23. A method to determine antimalarial activity of a compound by inhibiting the elongation of fatty acid synthesis in a malaria parasite wherein the said method comprising demonstration of the inhibition of fatty acid synthesis in the cell free fatty acid synthesis system of a malaria parasite by estimating the amount of radioactively labeled malonyl-CoA incorporated into fatty acids or lipids or by analyzing the type of fatty acids synthesized by a chromatographic method.

24. A method to determine the ability of any compound to inhibit the elongation of fatty acid synthesis in malaria parasite by demonstrating the inhibition of fatty acid synthesis in the cell free fatty acid synthesis system of malaria parasite by (a) estimating the incorporation, in the amount of radioactively labeled acetate or other products thereof such as acetyl-CoA, butyryl-CoA, crotonyl-CoA, malonyl-CoA etc. or acetyl-ACP, butyryl-ACP, crotonyl-ACP, malonyl-ACP etc. (ACP; Acyl Carrier Protein) into fatty acids or lipids (b) by analyzing the type of fatty acids synthesized by a chromatographic method.

25. (Once amended) A method of treatment of malaria in a subject, wherein the said method comprising the administration of the composition as claimed in claim 7 to the said subject through a route selected from the group consisting of oral, intramuscular, intradermal, intraperitoneal, intravenous, intra-arterial and subcutaneous.

26. Use of a compound for inhibiting the elongation of fatty acid synthesis in a malaria parasite.

A drug based on the use of a compound for inhibiting the elongation of fatty acid synthesis in malaria parasite.

Use of an inhibitor of fatty acid synthesis or its pharmaceutically acceptable derivative(s) as an antimalarial agent.

27. Use of an inhibitor of fatty acid synthesis or its pharmaceutically acceptable derivatives as an antimalarial agent either alone or in combination with one or more known antimalarials along with a pharmaceutically acceptable adjuvant or a diluent or a carrier.

28. Use of hydroxydiphenyl ether class of chemicals or a pharmaceutically acceptable derivative thereof, as an antimalarial agent.

29. Use of hydroxydiphenyl ether class of chemicals or a pharmaceutically acceptable derivative thereof as antimalarial agents along with a pharmaceutically acceptable adjuvant, or diluent or a carrier.

30. A method for the screening or the designing of drugs using the activity of enoyl-ACP reductase, as a target for treating a malarial infection comprising of the spectrophotometric measurement of its activity using crotonyl-CoA, crotonyl-ACP or other intermediates of fatty acid synthesis as substrates.

31. A method for the screening of drugs using the activity of enoyl-ACP reductase as a target for treating a malarial infection comprising the use of a molecular model of enoyl-ACP reductase of a malarial parasite.

32. An antimalarial drug based on inhibiting the activity of enoyl-ACP reductase in *P. falciparum*.
33. Use of triclosan to treat infection by *P. falciparum*, an apicomplexan parasite.
34. Use of triclosan to treat infection caused by an apicomplexan parasite.
35. Use of a hydroxydiphenyl ether in combination with a biocide for treating a malarial condition.